



Docket No. 1919/62814-A/JPW/GJG/JH

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Timothy Norris et al.
Serial No. : 09/711,272
Filed : November 9, 2000
For : Stable Polymorph of N-(3-Ethylphenyl)-6,7-Bis(2-methoxyethoxy)-4-Quinazolinamine Hydrochloride, Methods of Production and Uses Thereof.

1185 Avenue of the Americas
New York, New York 10036
June 29, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

(contained in a total of five volumes of references)

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicant would like to direct the Examiner's attention to the following disclosures, which are listed on Form PTO-1449 (**Exhibit A**). Copies of the disclosures listed below as items 1-87 are attached hereto as **Exhibits 1-87**, respectively:

1. U.S. Patent No. 4,139,561 (Onopchenko et al.) issued February 13, 1979 (**Exhibit 1**);
2. U.S. Patent No. 4,216,341 (Onopchenko et al.) issued August 5, 1980 (**Exhibit 2**);
3. U.S. Patent No. 4,219,679 (Onopchencko et al.) issued August 26, 1990 (**Exhibit 3**);
4. U.S. Patent No. 4,255,313 (Antonoplos et al.) issued March 10, 1981 (**Exhibit 4**);

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5. U.S. Patent No. 4,305,751 (Sabourin et al.) issued December 15, 1981 (**Exhibit 5**);
6. U.S. Patent No. 4,322,420 (Kobayashi et al.) issued March 30, 1982 (**Exhibit 6**);
7. U.S. Patent No. 4,943,533 (Mendelsohn et al.) issued July 24, 1990 (**Exhibit 7**);
8. U.S. Patent No. 5,089,499 (Barker et al.) issued February 18, 1992 (**Exhibit 8**);
9. U.S. Patent No. 5,256,781 (Primeau et al.) issued October 26, 1993 (**Exhibit 9**);
10. U.S. Patent No. 5,457,105 (Barker) issued October 10, 1995 (**Exhibit 10**);
11. U.S. Patent No. 5,475,001 (Barker) issued December 12, 1995 (**Exhibit 11**);
12. U.S. Patent No. 5,580,870 (Barker) issued December 3, 1996 (**Exhibit 12**) ;
13. U.S. Patent No. 5,616,582 (Barker) issued April 1, 1997 (**Exhibit 13**);
14. U.S. Patent No. 5,639,881 (Skibo et al.) issued June 17, 1997 (**Exhibit 14**);
15. U.S. Patent No. 5,654,307 (Bridges et al.) issued August 5, 1997 (**Exhibit 15**);

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16. U.S. Patent No. 5,686,458 (Lee et al.) issued November 11, 1997 (**Exhibit 16**);
17. U.S. Patent No. 5,707,992 (Webber et al.) issued January 13, 1998 (**Exhibit 17**);
18. U.S. Patent No. 5,710,145 (Engel et al.) issued January 20, 1998 (**Exhibit 18**);
19. U.S. Patent No. 5,747,498 (Schnur et al.) issued May 5, 1998 (**Exhibit 19**);
20. U.S. Patent No. 5,770,195 (Hudziak et al.) issued January 23, 1998 (**Exhibit 20**);
21. U.S. Patent No. 5,817,674 (Clemence et al.) issued October 6, 1998 (**Exhibit 21**);
22. U.S. Patent No. 5,821,246 (Brown et al.) issued October 13, 1998 (**Exhibit 22**);
23. U.S. Patent No. 5,948,784 (Fujiwara et al.) issued September 7, 1989 (**Exhibit 23**);
24. U.S. Patent No. 6,004,979 (Clemence et al.) issued December 21, 1999 (**Exhibit 24**);
25. U.S. Patent No. 6,130,218 (Morsdorf et al.) issued October 10, 2000 (**Exhibit 25**);
26. Australian Patent No. AU 18422/92 filed June 22, 1992 (**Exhibit 26**);

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27. Australian Patent No. AU 31010/93 filed January 4, 1993
(**Exhibit 27**);
28. Australian Patent No. AU 38/13095 filed November 8, 1995
(**Exhibit 28**);
29. Canadian Patent No. CA 2,086,968 filed November 12, 1992
(**Exhibit 29**);
30. German Patent No. DE 2,936,705 filed September 11, 1979
(**Exhibit 30**);
31. European Patent No. EP 0 498 723 filed February 5, 1992
(**Exhibit 31**);
32. European Patent Application Publication No. EP 0 520 722 A1
published December 30, 1992 (**Exhibit 32**);
33. European Patent No. EP 0 566 226 B1 filed January 15, 1993
(**Exhibit 33**);
34. European Patent Application Publication No. EP 0 579 496 A1
published January 19, 1994 (**Exhibit 34**);
35. European Patent Application Publication No. EP 0 602 851
A1 published June 22, 1994 (**Exhibit 35**);
36. European Patent Application Publication No. EP 0 635 498 A1
published January 25, 1995 (**Exhibit 36**);
37. European Patent Application Publication No. EP 0 635 507 A1
published January 25, 1995 (**Exhibit 37**);

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38. European Patent Application Publication No. EP 0 667 165 A1 published August 16, 1995 (**Exhibit 38**);
39. European Patent Application Publication No. EP 0 787 722 A1 published August 6, 1997 (**Exhibit 39**);
40. Japanese Patent No. JP 1048048 filed August 19, 1987 (**Exhibit 40**);
41. Japanese Patent No. JP 5208911 filed June 22, 1992 (**Exhibit 41**);
42. Japanese Patent No. JP 6192235 filed July 15, 1993 (**Exhibit 42**);
43. Japanese Patent No. JP 6205969 filed July 3, 1985 (**Exhibit 43**);
44. Japanese Patent No. JP 6336481 filed December 3, 1993 (~~**Exhibit 44**~~);
45. Japanese Patent No. JP 7101941 filed September 30, 1993 (**Exhibit 45**);
46. Japanese Patent No. JP 7118266 filed January 28, 1994 (**Exhibit 46**);
47. Japanese Patent No. JP 7126255 filed September 7, 1994 (**Exhibit 47**);
48. Japanese Patent No. JP 7188244 filed October 7, 1994 (**Exhibit 48**);

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49. Japanese Patent No. JP 7309873 filed November 9, 1992
(**Exhibit 49**);
50. Japanese Patent No. JP 8099962 filed July 15, 1993 (**Exhibit 50**);
51. Japanese Patent No. JP 8151377 filed November 25, 1994
(**Exhibit 51**);
52. Japanese Patent No. JP 9165385 filed August 25, 1995
(**Exhibit 52**);
53. Japanese Patent No. JP 9221478 filed February 4, 1997
(**Exhibit 53**);
54. New Zealand Patent No. NZ 0245662 filed January 15, 1993
(**Exhibit 54**);
55. Russian Patent No. RU 2127263 filed January 15, 1993
(**Exhibit 55**);
56. PCT International Application Publication No. WO 92/20642
published November 26, 1992 (**Exhibit 56**);
57. PCT International Application Publication No. WO 95/03283
published February 2, 1995 (**Exhibit 57**);
58. PCT International Application Publication No. WO 95/15758
published June 15, 1995 (**Exhibit 58**);-
59. PCT International Application Publication No. WO 96/09294
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60. PCT International Application Publication No. WO 96/15118
published May 23, 1996 (**Exhibit 60**);
61. PCT International Application Publication No. WO 96/28430
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62. PCT International Application Publication No. WO 96/30347
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63. PCT International Application Publication No. WO 96/40210
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64. PCT International Application Publication No. WO 97/03069
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65. PCT International Application Publication No. WO 97/30035
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66. PCT International Application Publication No. WO 97/32856
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67. PCT International Application Publication No. WO 97/41896
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68. PCT International Application Publication No. WO 98/13354
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69. PCT International Application Publication No. WO 99/03803
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70. PCT International Application Publication No. WO 99/55683
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71. PCT International Application Publication No. WO 99/60023 published November 25, 1999 (**Exhibit 71**);
72. PCT International Application Publication No. WO 00/31048 published February 6, 2000 (**Exhibit 72**);
73. Agharkar, S., et al., "Enhancement of Solubility of Drug Salts by Hydrophilic Counterions: Properties of Organic Salts of an Antimalarial Drug," *Journal of Pharmaceutical Sciences* **1976**, Vol. 65, No. 5, p.p. 747-749 (**Exhibit 73**);
74. Berge, S., et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences* **1977**, Vol. 66, No. 1, p.p. 1-19 (**Exhibit 74**);
75. Bleicher, L., et al., "Aryl- and Hetero-Alkyne Coupling Reactions Catalyzed by Palladium on Carbon and CuI in an Aqueous Medium," *Synlett* **1995**, November, p.p. 1115-1116 (**Exhibit 75**);
76. Bleicher, L., et al., "A Practical and Efficient Synthesis of the Selective Neuronal Acetylcholine-Gated Ion Agonist (S)-(-)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine Maleate (SIB-1508Y)," *Journal of Organic Chemistry* **1998**, Vol. 63, No. 4, p.p. 1109-1118 (**Exhibit 76**);
77. Botros, S., et al., "Synthesis of Certain Nitro-quinazoline Derivatives Structurally Related to Some Chemotherapeutic Agents," *Egypt. J. Pharm. Sci.* **1972**, Vol. 13, No. 1, p.p. 11-21 (**Exhibit 77**);

78. Cerny, A., "Solvolysis of Some 1-(8a-ergolyinyl)-3,3-Diethylureas and Their Salts," *Collection-Czechoslovak Chem. Commun.* **1987**, Vol. 52, p.p. 1331-1339 (**Exhibit 78**);
79. Hussain, M., et al., "Parenteral Formulation of the Kappa Agonist Analgesic, DuP 747, via Micellar Solubilization," *Pharmaceutical Research* **1992**, Vol. 9, No. 6, p.p. 750-752 (**Exhibit 79**);
80. Moyer, J., et al., "Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase," *Cancer Research* **1997**, Vol. 57, p.p. 4838-4848 (**Exhibit 80**);
81. Norris, T., et al., "Discovery of a New Stable Polymorph of 4-(3-ethynylphenylamino)-6,7-bis(2-methoxy-ethoxy)-quinazolinium Methanesulfonate Using Near-Infrared Spectroscopy to Monitor Form Change Kinetics," *J. Chem. Soc., Perkin Trans.* **2000**, Vol. 2, p.p. 1233-1236 (**Exhibit 81**);
82. Onopchenko, et al., "Selective Catalytic Hydrogenation of Aromatic Nitro Groups in the Presence of Acetylenes. Synthesis of (3-Aminophenyl)acetylene via Hydrogenation of Dimethylcarbinol Substituted (3-Nitrophenyl)acetylene over Heterogeneous Metallic Ruthenium Catalyst," *Journal of Organic Chemistry* **1979**, Vol. 44, No. 8, p.p. 1233-1236 (**Exhibit 82**);
83. Pollack, V., et al., "Inhibition of Epidermal Growth Factor Receptor-Associated Tyrosine Phosphorylation in Human Carcinomas with CP-358,774: Dynamics of Receptor Inhibition In Situ and Antitumor Effects in Athymic Mice," *Journal of*

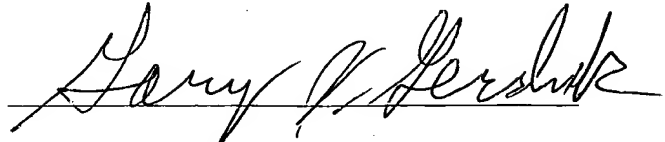
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84. Rosenberg, S., et al., "Studies Directed toward the Design of Orally Active Renin Inhibitors. 2. Development of the Efficacious, Bioavailable Renin Inhibitor (2S)-2-Benzyl-3-[[[(1-methylpiperazin-4-yl)sulfonyl]propionyl]-3-thiazol-4-yl-L-alanine Amide of (2S, 3R, 4S)-2-Amino-1-cyclohexyl-3, 4-dihydroxy-6-methylheptane (A-72517)," *J. Med. Chem.* 1993, Vol. 36, p.p. 460-467 (**Exhibit 84**);
85. Smaill, J., et al., "Tyrosine Kinase Inhibitors. 17. Irreversible Inhibitors of the Epidermal Growth Factor Receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides Bearing Additional Solubilizing Functions," *J. Med. Chem.* 2000, Vol. 43, p.p. 1380-1397 (**Exhibit 85**);
86. Spurlock, C., "Increasing Solubility of Enoxacin and Norfloxacin by Means Salt Formation," *Journal of Parenteral Science and Technology* 1986, Vol. 40, No. 2, p.p. 70-72 (**Exhibit 86**);
87. Takalo, H., et al., "Synthesis of Some Substituted Dimethyl and Diethyl 4-(Phenylethynyl)-2,6-pyridine-dicarboxylates," *Acta Chemica Scandinavica*, Vol. B42, p.p. 448-454 (**Exhibit 87**);

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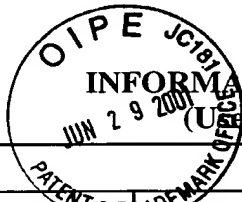
authorization is hereby given to charge the amount of any such
fee to Deposit Account No. 03-3125.

Respectfully submitted,

A handwritten signature in dark ink, appearing to read "Gary J. Gershik", is written over a horizontal line.

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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1919/62814-ASerial No.
09/711,272

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

Applicants
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	CA 2 0 8 6 9 6 8	11/12/92	Canadian				
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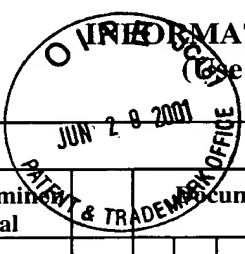
	Agharkar, S., et al., "Enhancement of Solubility of Drug Salts by Hydrophilic Counterions: Properties of Organic Salts of an Antimalarial Drug," <i>Journal of Pharmaceutical Sciences</i> 1976, Vol. 65, No. 5, p.p. 747-749 (Exhibit 73)
	Berge, S., et al., "Pharmaceutical Salts," <i>Journal of Pharmaceutical Sciences</i> 1977, Vol. 66, No. 1, p.p. 1-19 (Exhibit 74)
	Bleicher, L., et al., "Aryl- and Hetero-Alkyne Coupling Reactions Catalyzed by Palladium on Carbon and CuI in an Aqueous Medium," <i>Synlett</i> 1995, November, p.p. 1115-1116 (Exhibit 75)

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Applicants: Timothy Norris et al.
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Exhibit A

Form PTO-1449		U.S. Department of Commerce Patent and Trademark Office		Atty. Docket No.		Serial No.		
				Applicants				
				Filing Date		Group		
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								Yes No
		EP 0 6 3 5 5 0 7	1/25/95	European Patent Office				
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		Bleicher, L., et al., "A Practical and Efficient Synthesis of the Selective Neuronal Acetylcholine-Gated Ion Agonist (S)-(-)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine Maleate (SIB-1508Y)," <i>Journal of Organic Chemistry</i> 1998 , Vol. 63, No. 4, p.p. 1109-1118 (Exhibit 76)						
		Botros, S., et al., "Synthesis of Certain Nitro-quinazoline Derivatives Structurally Related to Some Chemotherapeutic Agents," <i>Egypt. J. Pharm. Sci.</i> 1972 , Vol. 13, No. 1, p.p. 11-21 (Exhibit 77)						
		Cerny, A., "Solvolysis of Some 1-(8a-ergolyinyl)-3,3-Diethylureas and Their Salts," <i>Collection-Czechoslovak Chem. Commun.</i> 1987 , Vol. 52, p.p. 1331-1339 (Exhibit 78)						
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													Yes	No
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	Hussain, M., et al., "Parenteral Formulation of the Kappa Agonist Analgesic, DuP 747, via Micellar Solubilization," <i>Pharmaceutical Research</i> 1992 , Vol. 9, No. 6, p.p. 750-752 (Exhibit 79)
	Moyer, J., et al., "Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase," <i>Cancer Research</i> 1997 , Vol. 57, p.p. 4838-4848 (Exhibit 80)
	Norris, T., et al., "Discovery of a New Stable Polymorph of 4-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)quinazolinium Methanesulfonate Using Near-Infrared Spectroscopy to Monitor Form Change Kinetics," <i>J. Chem. Soc., Perkin Trans.</i> 2000 , Vol. 2, p.p. 1233-1236 (Exhibit 81)
	Onopchenko, et al., "Selective Catalytic Hydrogenation of Aromatic Nitro Groups in the Presence of Acetylenes. Synthesis of (3-Aminophenyl)acetylene via Hydrogenation of Dimethylcarbinol Substituted (3-Nitrophenyl) acetylene over Heterogeneous Metallic Ruthenium Catalyst," <i>Journal of Organic Chemistry</i> 1979 , Vol. 44, No. 8, p.p. 1233-1236 (Exhibit 82)

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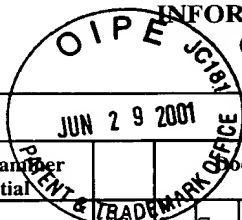
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	Pollack, V., et al., "Inhibition of Epidermal Growth Factor Receptor-Associated Tyrosine Phosphorylation in Human Carcinomas with CP-358,774: Dynamics of Receptor Inhibition In Situ and Antitumor Effects in Athymic Mice," <i>Journal of Pharmacology and Experimental Therapeutics</i> , 1999, Vol. 291, No. 2, p.p. 739-748 (Exhibit 83)
	Rosenberg, S., et al., "Studies Directed toward the Design of Orally Active Renin Inhibitors. 2. Development of the Efficacious, Bioavailable Renin Inhibitor (2S)-2-Benzyl-3-[[[(1-methylpiperazin-4-yl)sulfonyl]propionyl]-3-thiazol-4-yl-L-alanine Amide of (2S, 3R, 4S)-2-Amino-1-cyclohexyl-3, 4-dihydroxy-6-methylheptane (A-72517)," <i>J. Med. Chem.</i> 1993, Vol. 36, p.p. 460-467 (Exhibit 84)

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WO 9 7 3 2 8 5 6	09/12/97	PCT International					
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	Spurlock, C., "Increasing Solubility of Enoxacin and Norfloxacin by Means Salt Formation," <i>Journal of Parenteral Science and Technology</i> 1986 , Vol. 40, No. 2, p.p. 70-72 (Exhibit 86)
	Takalo, H., et al., "Synthesis of Some Substituted Dimethyl and Diethyl 4-(Phenylethynyl)-2,6-pyridine-dicarboxylates," <i>Acta Chemica Scandinavica</i> , Vol. B42, p.p. 448-454 (Exhibit 87)

EXAMINER

DATE CONSIDERED

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.